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Case report

Clinical and molecular characteristics in three families with biallelic mutations in *IGHMBP2*

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Abstract

Biallelic mutations in *IGHMBP2* cause spinal muscular atrophy with respiratory distress type 1 (SMARD1) or Charcot–Marie–Tooth type 2S (CMT2S). We report three families variably affected by *IGHMBP2* mutations. Patient 1, an 8-year-old boy with two homozygous variants: c.2T>C and c.861C>G, was wheelchair bound due to sensorimotor axonal neuropathy and chronic respiratory failure. Patient 2 and his younger sister, Patient 3, had compound heterozygous variants: c.983_987delAAGAA and c.1478C>T. However, clinical phenotypes differed markedly as the elder with sensorimotor axonal neuropathy had still unaffected respiratory function at 4.5 years, whereas the younger presented as infantile spinal muscular atrophy and died from relentless respiratory failure at 11 months. Patient 4, a 6-year-old girl homozygous for *IGHMBP2* c.449+1G>T documented to result in two aberrant transcripts, was wheelchair dependent due to axonal polyneuropathy. The clinical presentation in Patients 1 and 3 were consistent with SMARD1, whereas Patients 2 and 4 were in agreement with CMT2S.

Keywords: Axonal polyneuropathy; CMT2S; *IGHMBP2*; SMARD1; Spinal muscular atrophy

1. Introduction

Immunoglobulin mu-binding protein 2 (*IGHMBP2*) is a ubiquitously expressed DNA and RNA helicase [1–3]. Biallelic mutations in this gene result in degeneration of α-motor neurons in the brain stem and the anterior horns of the spinal cord, causing spinal muscular atrophy with respiratory distress type 1 (SMARD1; OMIM 604320) or Charcot–Marie–Tooth type 2S (CMT2S; OMIM 616155). IGHMBP2 is implicated in transcription [4,5], pre-mRNA processing [2,6], translation [5,7,8], and immunoglobulin class switching [2]. Mutated *IGHMBP2* is suggested to result in a deficiency of maturation of mRNAs in neurons, thereby leading to neuronal degeneration [1].

SMARD1 is characterized by infantile onset severe axonal polyneuropathy and diaphragmatic paralysis [4,9–11]. Typically SMARD1 patients die within the first year of life due to respiratory failure [4,10,11]. However, the disease severity in SMARD1 may be variable, and juvenile onset of respiratory distress [12–15] with survival up to 20 years has been reported [14,16]. At the mild end of the *IGHMBP2* mutation disease spectrum, patients present with CMT2S, a sensorimotor axonal polyneuropathy, usually with less pronounced neurophysiological changes compared to SMARD1, relatively spared respiratory function, and longer survival [1,15,17].

Here we describe four individuals from three families with biallelic mutations in *IGHMBP2*. The common denominator for referral of these patients was gross motor delay. We identified four mutations in *IGHMBP2*. The clinical presentation in the patients varied from SMARD1 to CMT2S, even within one family. We also show for the first time that the *IGHMBP2* c.449+1G>T variant results in two aberrant

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transcripts, both containing a premature termination codon (PTC).

2. Case report

2.1. Clinical description

2.1.1. Family A

Patient 1, a boy, was the second child of healthy first-degree cousins of Pakistani origin (Fig. 1a). When assessed at a routine health check-up at 6 months, he was noted to be hypotonic with protrusion of the right side of his thorax. Motor development was significantly delayed and at 2.5 years he could only walk a few steps using an orthosis. He had distal muscular atrophy of the upper and lower extremities, hypermobile joints and absent reflexes. At 5 years he had profound distal weakness and poor head control. He was no longer able to sit or walk, and had become wheelchair dependent. He had dysphagia and a weak cough and suffered from chronic respiratory distress that required ventilatory support during sleep. From 5.5 years he was completely dependent on ventilatory support and also required a cough assist machine. At 6 years his extremities were paralyzed, except for preservation of some movement with his fingers. Feeding was difficult, necessitating a gastric feeding tube.

Neurophysiological examinations at 2 years showed lack of responses from both motor nerves (median, tibial and peroneal in his right extremities) and from the median sensory nerve. At the age of 5 years he still lacked both motor responses from the median, ulnar, tibial and peroneal nerves and sensory responses from the median, ulnar, sural and superficial peroneal nerves. However, there were responses from the sensory radial nerves (amplitude 3.0–5.2 μV and nerve conduction velocities (NCVs) 35–36 m/s). Needle-electromyography (EMG) of the anterior tibial and lateral vastus muscles at age 2 years and the lateral vastus and deltoid muscles at age 5 years showed spontaneous activity with fibrillation potentials in at least one muscle each time and at age 2 also some neurogenic motor unit potentials. However, due to muscle atrophy it was generally difficult to judge activity in the muscles. A biopsy of the sural nerve at 6 years showed lack of myelinated fibers. The results of these examinations were compatible with a pronounced sensorimotor axonal neuropathy. Ultrasound examination of his chest revealed reduced diaphragm motility. Echocardiography and cognitive function were normal.

2.1.2. Family B

Patients 2 and 3 were siblings, born to non-consanguineous healthy parents of Norwegian origin (Fig. 1b).

Patient 2, a boy, appeared normal at birth, but soon developed contractures of the Achilles tendons, progressing to pes cavus with forefoot adduction between 4 and 8 months. Although he learned to walk before 15 months, peripheral neurogenic problems persisted, making him dependent on orthosis for walking at 20 months. At this stage, atrophy of the calf muscles and weakness for dorsiflexion of the ankles were noted. The upper extremities had also become mildly affected with contractures of the fingers. The deep tendon reflexes were

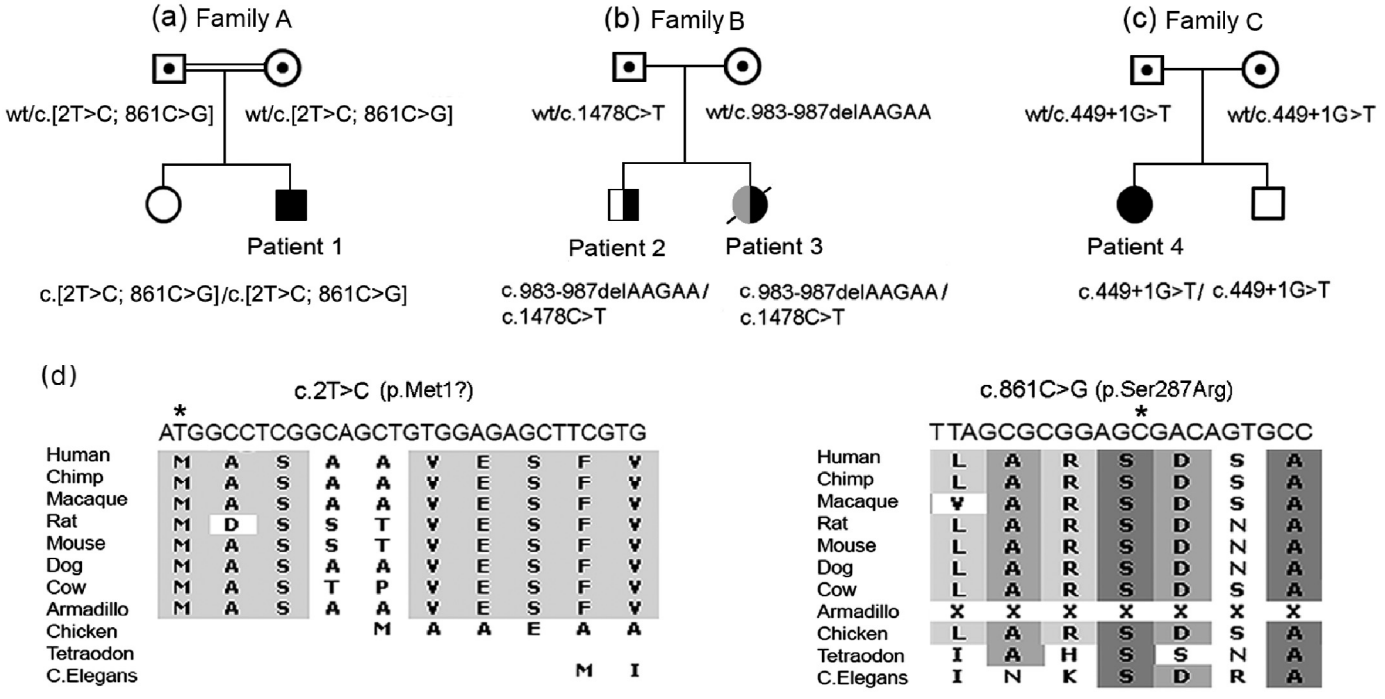

Fig. 1. a) Pedigree of family A showing the segregation of two variants in *IGHMBP2* c.2T>C and c.861C>G. Both *IGHMBP2* variants were found in *cis* in heterozygosity in the parents and in homozygosity in Patient 1. b) Pedigree of family B showing the segregation of the *IGHMBP2* c.1478C>T and c.983-987delAAGAA variants (indicated in black), parents were carriers. Patient 3 also had a *de novo* c.14092_14093insTA in *MLL2* (indicated in grey). c) Pedigree of family C showing the segregation of the *IGHMBP2* c.449+1G>T variant. d) Image from Alamut Visual Software (Rouen, France) showing the evolutionary conservation of the amino acid changes resulting from the two variants c.2T>C (p.1M?) and c.861C>G (p.Ser287Arg) in Patient 1 Family A (black stars).

absent. Pectus excavatum was noted at 4.5 years, but he had not shown signs of respiratory dysfunction.

Neurophysiological examination performed at 18 months showed pathologically low motor amplitudes from all nerves tested (right median 2.2mV, right ulnar 0.3 mV and the tibial nerves bilaterally 0.2-07 mV, no response from peroneal nerves). It was only possible to measure the NCV in the median nerve and this was slightly delayed (34.6 m/s; reference values for NCV used in this study are based on Miller and Kuntz [18]). Sensory nerve conduction velocities ranged between 38.5 m/s in the ulnar nerve (normal range between 13 and 24 months is 41.3–63.5 m/s) and 56.3 m/s in the median nerve, 38.7 m/s in the sural nerve and 57.3 m/s in the peroneal superficial nerve. The sensory amplitudes were also pathologically low, ranging from 3.6 to 3.9 μV in the median and ulnar nerves, respectively, and 2.9–3.6 μV in the sural and peroneal superficial nerves. EMG of the anterior tibial and lateral vastus muscles showed spontaneous activity. These findings suggested sensorimotor axonal polyneuropathy with motor nerve fibers more affected than sensory nerve fibers. This was confirmed by similar findings in a repeated neurophysiological examination less than 3 months later when EMG also showed chronic neurogenic findings in the anterior tibial muscles bilaterally. Ultrasound examination of the diaphragm at 3 years showed normal motility, and overnight monitoring of pO_2 and pCO_2 was also normal. His cognitive development was normal.

Patient 3, a girl, was born at 36 weeks of gestation after an uncomplicated pregnancy, with birth weight and length at the 3rd centiles, and head circumference 1 cm below the 3rd centile. She was admitted to the neonatal intensive care unit with feeding difficulties and hypotonia. She exhibited dysmorphic features that included widely spaced eyes, elongated palpebral fissures, long eyelashes, high-arched and interrupted eyebrows, fetal pads, and pectus excavatum, suspected to be due to Kabuki syndrome (OMIM 147920). She was hospitalized at 1 month due to feeding difficulties and at 5 months due to urosepsis. Motor development was severely delayed and at 8 months she could not crawl, whereas the deep tendon reflexes were difficult to elicit. When hospitalized due to a pulmonary infection at age 8 months, she showed paradoxical movements of the diaphragm, indicating muscle weakness. Upon the acute respiratory distress caused by the pulmonary infection, she developed a chronic respiratory failure with increasing need for ventilator support. Neurophysiological examinations were suggestive of motor axonal polyneuropathy with low motor amplitudes both for the median (1.1 mV) and ulnar nerve (2.2 mV) in the right upper extremity and for the tibial nerves bilaterally in the lower extremities (0.4–2.2 mV). The NCVs were within normal range (38.5–59 m/s). No motor responses were detected from the peroneal nerves bilaterally. Only two sensory nerves were examined, the right median and left peroneal superficial nerves, and they were within normal range for her age (amplitudes 15 and 4.7 respectively and NCV 48 and 40 m/s). EMG-recordings in the anterior tibial muscles bilaterally and from the left vastus and right deltoid muscles revealed no spontaneous activity. She died at 11 months due to chronic respiratory failure. Cerebral MRI was normal.

2.1.3. Family C

Patient 4, a girl, was the first child of healthy parents of Kurdish origin, reported to be unrelated (Fig. 1c).

She was referred from the public health station for children at 13 months due to delayed motor development, as she was hypotonic and could sit only with support. She walked with support at 22 months. On examination at 2 years, distal muscle atrophy, foot deformities with valgus positioning of the right foot, varus positioning of the left foot and hyperextension of the knees were observed. At 6 years, the deep tendon reflexes were noted to be absent and she required orthosis in order to stand and walk. She was easily fatigued and mostly wheelchair dependent. At the same age she was evaluated by cough peak expiratory flow (PEF), spirometry and nocturnal transcutaneous registration of carbon dioxide and oxygen saturation, showing a weak cough, but no signs of hypoventilation (movements of the diaphragm were not evaluated). She started to use a cough assist machine. Slow recovery from respiratory tract infections became evident. She underwent surgery for bilateral clubfeet. The ability to swallow liquids and solids was impaired to such an extent that she needed the insertion of a percutaneous gastric tube. Neurophysiological examination at 28 months showed low motor amplitudes in the right median (2.5 mV) and bilaterally in the tibial nerves (0.6 and 2.0 mV respectively) and with only a very small response (0.1 mV) in one of the two peroneal nerves tested. The conduction velocities were delayed, 38.7 m/s in the median nerve and from 25.1 to 28.7 m/s in the lower extremities. There was no sensory response from the sural nerve, but a slightly lowered response from the median nerve (5.9 μV) with a conduction velocity of 40 m/s. EMG from both anterior tibial muscles showed spontaneous activity and during voluntary activity there were a few neurogenic motor unit potentials. The findings were compatible with sensorimotor axonal polyneuropathy. Echocardiography and cognitive development were normal.

2.2. Molecular analyses

2.2.1. Family A

Whole exome sequencing (WES) was performed in Patient 1 and his parents. Data analysis assuming autosomal recessive mode of inheritance identified two homozygous variants in *IGHMBP2* (NM_002180.2): c.2T>C; p.Met1? (chr11:hg19.g:68,671,422 bp) and c.861C>G; p.Ser287Arg (chr11:hg19.g:68,682,440 bp) in the patient, while both parents were found to be heterozygous for both variants (Fig. 1a) (Complete list of gene variants is provided in Table S1). Additional experimental WES details are in Supplementary File S1. Sanger sequencing verified the variants (all primer sequences used in this study are given in Table S2). The c.2T>C variant was previously identified in two patients clinically presenting with CMT1 by targeted gene panel sequencing [19]. *IGHMBP2* c.2T>C alters the start codon and is predicted to abolish protein production. The variant was not reported in the ExAC database (http://exac.broadinstitute.org), including more than 60,000 exomes. The closest alternative in-frame initiation codon was found at p.338, which is likely to be too distant to be utilized [20], and if used it would result in protein truncation in the

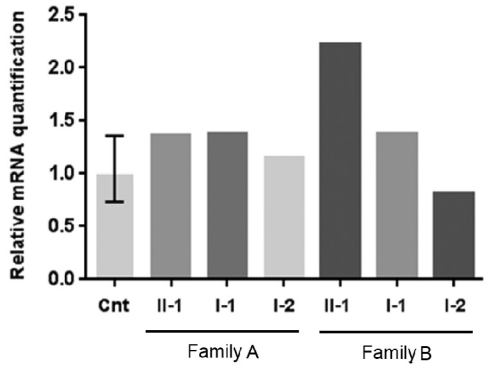

Fig. 2. Relative *IGHMBP2* mRNA levels measured by qRT-PCR in patients and parents in families A and B compared to the mean level in six controls, showing similar levels to controls in family A, and similar to increased levels in family B. Family A: Patient 1 with the two homozygous variants c.2T>C and c.861C>G and his parents heterozygous for both variants. Family B: Patient 2 with compound heterozygous variants c.1478C>T and c.983-987delAAGAA, and his heterozygous parents for the c.1478C>T and c.983-987delAAGAA variants, respectively. The mean level in the six controls is shown with 95% confidence interval.

crucial helicase domain [4,5,8]. Also, no alternative Kozak consensus sequence, 5′GCCGCCRMCATGGCG′3 (R = A or G and M = A or C), suggestive of an alternative start of translation [19,20], was found. In addition, another *IGHMBP2* variant, c.861C>G, was homozygous in Patient 1 and heterozygous in the parents. This missense variant in exon 6 changes a highly conserved amino acid in the helicase domain (Fig. 1d). ExAC database reported that *IGHMBP2* c.861C>G was found in heterozygosity in 55 out of 8255 individuals from South Asia (allele frequency 0.0033). Neither of the c.2T>C and c.861C>G variants were identified by Sanger sequencing in 166 healthy Pakistani individuals. In order to investigate if the c.2T>C variant would affect the transcript level, the *IGHMBP2* mRNA level was measured in Patient 1, his parents and six controls. The analysis showed similar levels in all individuals tested (Fig. 2).

2.2.2. Family B

Sanger sequencing of *IGHMBP2* was performed in Patient 3 based on the clinical presentation. A frameshift deletion in *IGHMBP2* exon 7, c.983_987delAAGAA; p.Lys328Thrfs46* (chr11:hg19.g:68,685,274-68,685,278), and a missense in *IGHMBP2* exon 10, c.1478C>T; p.Thr493Ile (chr11:hg19.g:68,701,322) were identified. Sanger sequencing showed that Patient 2 also had both variants, and that the c.983_987delAAGAA and c.1478C>T were of maternal and paternal origins, respectively (Fig. 1b). Both variants were previously reported in SMARD1 patients [5,10,12,21]. Patient 3 also had Kabuki syndrome (OMIM 147920), due to a *de novo* c.14092_14093insTA mutation in myeloid/lymphoid or mixed-lineage leukemia protein 2 *(MLL2)* (identified by Sanger sequencing). In order to investigate if the *IGHMBP2* c.983_987delAAGAA or c.1478C>T variants result in nonsense-mediated mRNA decay (NMD), the *IGHMBP2* mRNA levels were measured by qRT-PCR in Patient 2, his parents and six controls, showing a higher level in the patient and similar levels in parents and controls (Fig. 2).

2.2.3. Family C

In Patient 4 a homozygous *IGHMBP2* c.449+1G>T (chr11:hg19.g:68,675,806) splice donor site variant in intron 3 was identified by WES after analyzing a set of candidate genes (Table S3) based on clinical presentation. Sanger sequencing confirmed that Patient 4 was homozygous and the parents were heterozygous for the variant (Fig. 1c). The c.449+1G>T variant was previously reported in patients with SMARD1 and CMT2S [15,22]. Exons 3–5 in the *IGHMBP2* transcript were amplified by reverse-transcriptase PCR (RT-PCR) in Patient 4, her parents and six controls in order to identify possible aberrant transcripts resulting from the c.449+1G>T variant. The gel image showed a band representing the normal transcript in the controls (Fig. 3, band 1), which was absent in Patient 4. Instead the patient had two bands representing abnormal transcripts that were not present in the controls (Fig. 3, bands 2 and 3). All three bands were found also in the heterozygous parents (Fig. 3). Sanger sequencing

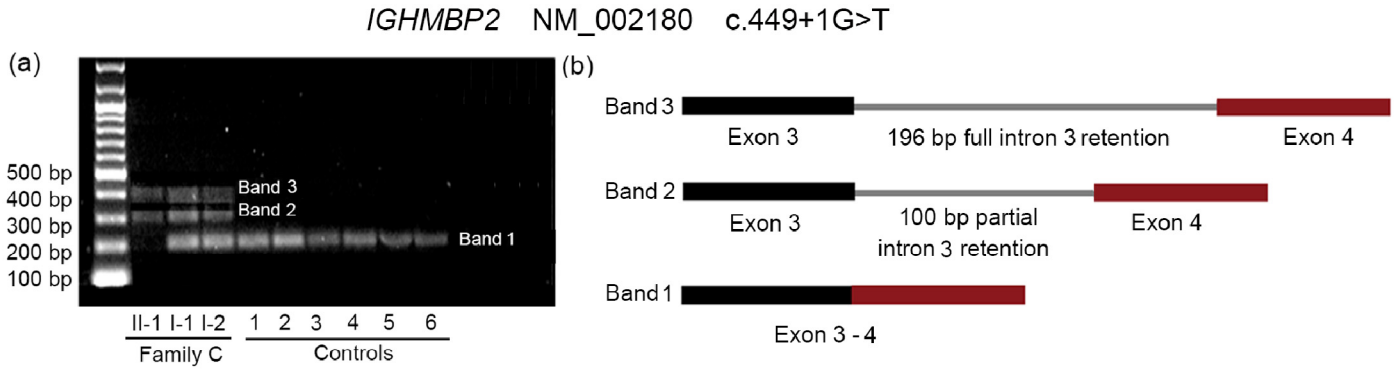

Fig. 3. a) Gel image of the RT-PCR products for exons 3–5 of the *IGHMBP2* transcript from the patient and parents from family C and six controls, showing that the band representing the normal transcript is absent in the patient with the homozygous splice variant c.449+1G>T (band 1), and instead the presence of bands 2 and 3 not seen in the controls. All three bands were detected in the parents with the heterozygous c.449+1G>T variant. This shows that the splice site variant c.449+1G>T results in two aberrant transcripts, and by Sanger sequencing of cDNA from bands 2 and 3, these were shown to have a full 196 bp intron 3 retention and a partial 100 bp intron 3 retention, respectively. b) Drawing of the content of bands 1, 2, and 3 based on Sanger sequencing results.

of band 2 in the patient showed a 100 bp intron 3 partial retention (chr11:hg19.g:68,675,806-68,675,906 bp), and Sanger sequencing of band 3 showed full 196 bp intron 3 retention (chr11:hg19.g:68,675,806-68,676,001 bp). Both aberrant transcripts have a PTC at c.449+2-c.449+4 (p.Lys150Asnfs*0), and are expected to result in NMD or a truncated protein.

The likely disease causing IGHMBP2 variants reported in the study are present in the Clinical Variant database (http://www.ncbi.nlm.nih.gov/clinvar/) with the following accession numbers: c.2T>C: SCV000255975; c.983_987delAAGAA: SCV000255976; c.1478C>T: SCV000255977; c.983_987delAAGAA: SCV000255978; c.1478C>T: SCV000255979; c.449+1G>T: SCV000255980.

3. Discussion

We identified four likely disease causing mutations in *IGHMBP2* in four patients from three independent families (c.2T>C, c.449+1G>T, c.1478C>T and c.983_987delAAGAA). Patient 1 (consanguineous family; Fig. 1a) had neurophysiological findings indicating a severe sensorimotor axonal neuropathy with onset of respiratory distress at 5 years, consistent with SMARD1. His neurophysiological findings could also be compatible with spinal muscular atrophy with an additional component of sensory neuropathy as previously described in SMARD1 [4,10]. At 8 years, he was wheelchair bound and in need of continuous respiratory support. He was found by WES to have a homozygous c.2T>C mutation in *IGHMBP2*, previously reported in two patients clinically presenting with CMT1 [19]. The lack of alterative in-frame initiation codons in the vicinity of the original initiation codon indicates that the c.2T>C variant likely abolishes protein translation, thus it was considered to be the cause of the disease in this patient. In addition, he had a second homozygous variant c.861C>G, which has been reported with an allele frequency of 0.0033 in the South Asian population in the ExAC database. Since SMARD1 is recognized as an extremely rare disorder [16], the relatively high allele frequency of the c.861C>G variant indicates it is a non-pathogenic rare genetic variant. In any case, the c.861C>G is not expected to have an impact on IGHMBP2 in Patient 1, because the c.2T>C variant likely abolishes protein production.

The siblings, Patients 2 and 3 (Fig. 1b), were compound heterozygous for two *IGHMBP2* mutations: c.1478C>T and c.983_987delAAGAA. There was considerable clinical variability as Patient 3 had SMARD1 and died at 11 months due to respiratory failure, whereas her brother, Patient 2, had a more typical axonal CMT2S phenotype without signs of respiratory distress at 4.5 years. In two families with *IGHMBP2* mutations a large degree of intrafamilial variability was described [15,23]. Intrafamilial variability may result from modifier variants in other genes or from variation in the residual level of IGHMBP1. Having Kabuki syndrome may have predisposed patient 3 to the pulmonary infection [24], which caused acute respiratory distress at age 8 months, after which the patient developed chronic respiratory distress.

The c.1478C>T was previously described in five patients from four families with compound heterozygous mutations [5,12,23,25]. The onset of respiratory distress ranged from 6 months to 10 years in four of these patients [5,23,25], and the fifth patient had normal respiratory function at 12 years [12]. A single patient with the c.983_987delAAGAA mutation in a homozygous state had SMARD1 and infantile onset of respiratory distress [10]. In our study, expression of the *IGHMBP2* mRNA indicated that the c.2T>C, c.983_987delAAGAA and c.1478C>T variants did not result in NMD (Fig. 2). This is in accordance with previous analysis showing that *IGHMBP2* mutations do not lead to reduced mRNA levels [12,26]. In the absence of NMD, the c.983_987delAAGAA is predicted to result in protein truncation, the c.2T>C is predicted to abolish protein translation and the c.1478C>T is predicted to directly affect the protein function.

Patient 4 (Fig. 1c), had predominantly axonal motor polyneuropathy and was mostly wheelchair dependent. At 6 years of age, only a weak cough indicated she might have mild respiratory muscle dysfunction. She was homozygous for *IGHMBP2* c.449+1G>T, previously reported in three patients: one with typical SMARD1 and onset of respiratory distress at 4 months [22] and two siblings with axonal sensory motor neuropathy, one with late-onset respiratory distress at 15 years, and one still without respiratory problems at 22 years [15]. *IGHMBP2* c.449+1G>T is a rare variant, since it is not reported in the ExAC database (search October 21, 2015), but it was found in two consanguineous families, one from Lebanon [15] and one from Kurdistan [22] (similar ethnicity as family C). This variant may therefore have a founder in the Middle East. In this report we show that *IGHMBP2* c.449+1G>T variant results in a full intron 3 retention, in addition to a previously described partial intron 3 retention [15] (Fig. 3), both predicted to result in NMD or a truncated protein with lack of function.

Two of our patients presented with SMARD1 (Patients 1 and 3), whereas the clinical phenotypes in the other two patients were in agreement with CMT2S (Patients 2 and 4), but late onset of respiratory distress cannot be excluded. However, prognostication based on the genotype is difficult, as neurophysiological findings overlap [1,15,22], and respiratory distress may present at a substantially later age, or even not occur at all [14,15].

4. Conclusion

Our study confirms that biallelic *IGHMBP2* mutations either may cause SMARD1 or CMT2S. In fact, phenotypic diversity may occur within the same family, as identical compound heterozygous mutations in siblings segregated as SMARD1 and CMT2S, exhibiting the severe and moderate phenotypes of the disease spectrum. We did not detect NMD of *IGHMBP2* mRNA resulting from the c.2T>C, c.983_987delAAGAA or c.1478C>T variants, indicating these variants affect the protein level or function directly. The *IGHMBP2* c.449+1G>T variant was shown to result in two aberrant transcripts, which may be degraded by NMD or alternatively produce a truncated protein.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2016.06.457.

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